Safety of Food Oral Immunotherapy

What We Know, and What We Need to Learn

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KEYWORDS

• Allergy • Food • Immunotherapy • Oral immunotherapy • Safety

KEY POINTS

- Compared with food avoidance, oral immunotherapy (OIT) for food allergy is associated with a higher incidence rate and risk of adverse reactions, including anaphylaxis.
- The lack of consistency in reporting adverse events in food OIT studies is the major limitation to establish precisely the safety profile, and therefore, an international consensus on safety reporting for OIT is needed.
- The analysis of large pooled clinical data sets and biological samples with integrated omics approaches is needed to identify risk factors and biomarkers associated with safety.
- The needs and opinions of patients/families on OIT should be taken into account for the management.
- It is absolutely necessary to stratify patients' risk of adverse reactions in order to manage them adequately with individualized care pathways.

INTRODUCTION

Food allergy (FA) has become a significant medical problem for which avoidance of the culprit foods and use of rescue medication in the event of an allergic reaction

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Immunol Allergy Clin N Am 40 (2020) 111–133
https://doi.org/10.1016/j.iac.2019.09.013 **immunology.theclinics.com**

are recommended as the "standard of care."[1] In the last 2 decades, considerable research has been done on immunotherapy for FA with the aim of providing a therapy with a disease-modifying effect. Several routes of administration have been investigated, including subcutaneous, oral, sublingual, and epicutaneous ones. The largest body of evidence is on oral immunotherapy (OIT), which consists of the oral administration of progressively increasing doses of the food allergen until reaching a target dose (up-dosing phase) that is then taken regularly (maintenance phase).[2] Although the quality of studies performed is heterogeneous and the number of treated patients is limited, recent systematic reviews and metaanalysis[2,3] have shown that OIT is able to produce desensitization, in other words, to increase the threshold of reactivity to the food, provided the patient maintains the regular intake of the food allergen dose. In some individuals, this lack of reactivity to the food is maintained even after a period of cessation of exposure, a status known as sustained unresponsiveness (or remission).[4]

The evidence that OIT is able to induce desensitization has challenged the "standard of care" in FA, opening the gate to OIT in the management of (some) food allergic patients. However, OIT is associated with a significant number of adverse events, including adverse reactions (AR) directly related to the immunotherapy,[2,3] and this safety concern is at present the major barrier for OIT to become a therapeutic option in clinical practice.

In this article, the authors review the current evidence on safety of OIT (focusing on AR), address the limitations and gaps in the knowledge, and discuss some alternatives to fill the gaps in this quickly evolving area.

SAFETY OF FOOD ORAL IMMUNOTHERAPY: WHAT IS KNOWN

OIT has the inherent risk of producing AR that can go from mild oral symptoms to anaphylaxis. Frequency of reactions is higher during the up-dosing phase performed in the clinical setting. However, reactions may also appear at home to a dose previously tolerated in the clinic during the up-dosing, and even in the maintenance phase to doses tolerated previously for weeks or months. Patients and their families should be trained in the recognition and management of AR, including the early self-administration of epinephrine in anaphylaxis.[4] Reactions are the main reason for discontinuation. A few cases of severe, life-threatening anaphylaxis have been published,[5–8] but to the best of the authors' knowledge, no fatalities have been reported so far.

Evidence from Systematic Reviews and Metaanalysis

Safety aspects of OIT have been studied in 2 recent systematic reviews and metaanalyses. Nurmatov and colleagues[2] searched publications until March 31, 2016 on allergen immunotherapy for any FA administered through oral (OIT), sublingual (SLIT), epicutaneous, or subcutaneous (SCIT) routes. Thirty-one studies with 1259 participants were included: 25 randomized clinical trials (RCT) and 6 nonrandomized controlled clinical trials (CCT). OIT was studied in 18 RCTs and in 5 CCTs, and the FAs most commonly treated were milk, egg, and peanut in 16, 11, and 7 studies, respectively. The occurrence of local reactions (LR) (minor oropharyngeal/gastrointestinal [GI] reactions, perioral rash) and systemic reactions (SR) was analyzed. Because of heterogeneity in reporting adverse events, only 5 OIT trials (on milk 3, on egg 1, and on peanut 1) with a total number of 150 participants could be pooled in the metaanalysis of SR. In the metaanalysis of LR, 7 studies were pooled (3 on milk, 3 on egg, and 1 on milk and egg OIT) with 319 total participants. Despite this limited number of studies and patients treated, an increased risk of reactions was shown during OIT, both local

(risk ratio [RR] of not experiencing a reaction in controls 2.12, 95% confidence interval [CI] 1.50–3.0) and systemic (RR of not experiencing a reaction in controls 1.16, 95% CI 1.03–1.30). Subgroup analysis showed an increased risk for SR in milk OIT, an increased risk for LR in milk and egg OIT, and that both conventional and rush protocols were associated with an increased risk of LR.

In the systematic review of Chu and colleagues,[3] published and unpublished RCTs comparing OIT for peanut allergy with placebo or avoidance were searched until December 6, 2018. Twelve studies (8 published between 2011 and 2018 and 4 unpublished) were included with 1041 participants, 767 from trials with proprietary formulations and 551 from a single phase 3 pivotal study.[9] The metaanalysis showed that peanut OIT increases anaphylaxis risk (RR 3.12, 95% CI 1.76–5.55), anaphylaxis frequency (incidence rate ratio 2.72, 95% CI 1.57–4.72), epinephrine use (RR 2.21, 95% CI 1.27–3.83), and serious adverse events (RR 1.92, 95% CI 1.0–3.66). When involvement of different organs/systems was analyzed, OIT increased the risk of having GI, mucocutaneous, and upper and lower respiratory reactions. These results were not modified by the OIT regimen (proprietary formulation or not, starting and target dose, treatment duration), or phase (buildup or maintenance), median participant age, and peanut threshold of reactivity in the entry oral food challenge.

Heterogeneity in Reporting Formats of Adverse Reactions in Oral Immunotherapy Studies

There is a high heterogeneity in the reporting formats of adverse events in OIT studies. It emerged already in the metaanalysis of Nurmatov[2] and reduced considerably the number of studies used in the quantitative synthesis. There is not yet a specific guideline on safety reporting of OIT in FA, and the proposed grading systems for SR in SCIT for nonfood allergens (reviewed in Ref.[9]) have not been applied in food OIT. Furthermore, there is considerable variability between systems used to grade SR in SCIT,[9] and food allergic reactions,[10] which, it is hoped, may be overcome with recent initiatives to harmonize this field.[11,12]

The authors have reviewed 52 studies for this article,[7–62] including 34 RCT, 10 CCT, and 8 real-life studies (RLS), dealing with peanut (n = 16), milk (n = 22), egg (n = 17), walnut (n = 1), sesame (n = 1), and wheat (n = 1) OIT (**Tables 1** and **2**).

In 64% of the studies reviewed, at least 80% of participants reached the target maintenance dose (mean 81.8%, range 21%–100%), and 0% to 36% (mean 11%) were withdrawn for AR. The frequency of patients with a certain AR is given in 84% of studies, whereas the total number of doses and the reaction rate per dose are provided in 40% and 45% of the studies, respectively. Only 40% report reactions separately per protocol phase, and there is scarce information on reactions in the long-term maintenance, because it is not covered within the time-frame of most RCT and CCT studies (**Tables 3** and **4**).

Severity grading of AR is done in 71% of articles reviewed (**Tables 5** and **6**) with different nonequivalent systems,[9,10] impairing comparisons across studies. Some trials present the frequency of severity graded reactions,[21,23,26,27,32,35,40,53,62] sometimes also depicted by phase.[7,17,26,27,31,37,48,52]

The authors have extracted the frequency of oropharyngeal, skin, GI, upper and lower respiratory reactions, and anaphylaxis (see **Tables 5** and **6**). Studies frequently provide the information in this line, per target organ/system involved, although some provide frequency of individual symptoms. Oral symptoms are sometimes excluded from the safety reporting, and upper and lower respiratory involvement may be presented in a single category (respiratory), with the consequent loss of information of the frequency of lower airway reactions, which are clinically relevant side effects.

Table 1
Characteristics of peanut, walnut, sesame, and wheat oral immunotherapy studies reviewed

			Participants			Intervention Group		Control Group	
Study	Country	Design	N	Age Range (y)	Female (%)	OIT	N	Comparator	N
Varshney et al,[14] 2011	USA	RDBPCT	28	2–10	36	Peanut	19	Placebo	9
Anagnostou et al,[15] 2014	UK	Crossover RCT	99	7–16	29	Peanut	49	Avoidance[a]	50
Tang et al,[16] 2015	Australia	RDBPCT	62	1–10	40	Peanut + probiotic	31	Placebo	31
Narisety et al,[17] 2015	USA	RDBPCT	21	6–21	48	Peanut	10	Peanut SLIT[a]	11
Kukkonen et al,[7] 2017	Finland	CCT	60	6–18	42	Peanut	39	Avoidance	21
Vickery et al,[18] 2017	USA	RCT	37	9–36 mo	31	Peanut low and high dose	37	Avoidance (historical cohort)	154
Bird et al,[19] 2018	USA	RDBPCT	55	4–26	35	Peanut	29	Placebo	26
Fauquert et al,[20] 2018	France	RDBPCT	30	12–18	27	Peanut	21	Placebo	9
Nagakura et al,[21] 2018	Japan	CCT	34	5–18	26	Peanut	24	Avoidance	10
Vickery et al,[13] 2018	USA, Canada, Europe	RDBPCT	555	4–55	43	Peanut	416	Placebo	139
Nachshon et al,[22] 2018	Israel	RLS	145	≥4	38	Peanut	145		
Blumchen et al,[23] 2019	Germany	RDBPCT	62	3–17	39	Peanut	31	Placebo	31
Reier-Nilsen et al,[24] 2019	Norway	RCT	77	5–15	43	Peanut	57	Avoidance	20
Wasserman et al,[25] 2019	USA	RLS	270	4–18	40	Peanut	270		
Soller et al,[26] 2019	Canada	RLS	270	9–71 mo	41	Peanut	270		
MacGinnitie et al,[27] 2017	USA	RDBPCT	37	6–19	41	Peanut + omalizumab	29	Peanut OIT + placebo	8
Elizur et al,[28] 2019	Israel	CCT	73	4–20	30	Walnut	55	Avoidance	18
Nachshon et al,[29] 2019	Israel	CCT	75	≥4	36	Sesame	60	Avoidance	15
Nowak-Węgrzyn et al,[30] 2019	USA	crossover RDBPCT	46	4–30	22	Wheat low vs high dose	23	Placebo	23

Abbreviation: RDBPCT, randomized double-blind placebo-controlled trial.
[a] Start OIT after avoidance or SLIT.

Table 2
Characteristics of milk and egg oral immunotherapy studies reviewed

			Participants			Intervention Group		Control Group	
Study	Country	Design	N	Age Range (y)	Female (%)	OIT	N	Comparator	N
Burks et al,[31] 2012	USA	RDBPCT	55	5–11		Egg	40	Placebo	15
Dello Iacono et al,[32] 2013	Italy	RCT	20	5–11	50	Egg	10	Avoidance	10
Fuentes-Aparicio et al,[33] 2013	Spain	RCT	72	4–15	25	Egg	40	Avoidance	32
Meglio et al,[34] 2013	Italy	RCT	20	≥4	40	Egg	10	Avoidance	10
Vazquez-Ortiz et al,[35] 2014	Spain	CCT	82	5–18	51	Egg	50	Avoidance	32
Caminiti et al,[36] 2015	Italy	RDBPCT	31	4–11	75	Egg	17	Placebo	14
Escudero et al,[37] 2015	Spain	RCT	61	5–17	37	Egg	30	Avoidance	31
Pérez-Rangel et al,[38] 2017	Spain	RCT	33	5–18	45	Egg	19	Avoidance[a]	14
Giavi et al,[39] 2016	Greece, Italy, Switzerland	RDBPCT	29	1–5.5	31	Egg	15	Placebo	14
Itoh-Nagato et al,[40] 2018	Japan	RCT	45	5–15	27	Egg	45	Avoidance[a]	22
Machinena et al,[41] 2019	Spain	RLS	43	>5	30	Egg	43		
Skripak et al,[42] 2008	USA	RDBPCT	20	6–17	40	Milk	13	Placebo	7
Longo et al,[43] 2008	Italy	RCT	60	5–17	35	Milk	30	Avoidance	30
Caminiti et al,[44] 2009	Italy	RDBPCT	13	5–10	38	Milk	10	Placebo	3
Pajno et al,[45] 2010	Italy	RSBPCT	30	4–10	43	Milk	15	Placebo	15
Martorell et al,[46] 2011	Spain	RCT	60	2–3	43	Milk	30	Avoidance	30
Salmivesi et al,[47] 2013	Finland	RDBPCT	28	6–14	57	Milk	18	Placebo	10
Vázquez-Ortiz et al,[48] 2013	Spain	RLS	81	5–18	38	Milk	81		

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Table 2
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			Participants			Intervention Group		Control Group	
Study	Country	Design	N	Age Range (y)	Female (%)	OIT	N	Comparator	N
Lee et al,[49] 2013	Korea	RCT	31	7–12 mo	50	Milk	16	Avoidance	15
García-Ara et al,[50] 2013	Spain	CCT	55	4–14	37	Milk	36	Avoidance	19
Martínez-Botas et al,[51] 2015	Spain	CCT	32	4–7	32	Milk	25	Avoidance	7
Yanagida et al,[52] 2015	Japan	CCT	37	≥5	31	Milk	12	Avoidance[a]	25
Wood et al,[53] 2016	USA	RDBPCT	57	7–32	30	Milk + omalizumab	28	Milk OIT + placebo	29
Takahashi et al,[54] 2017	Japan	RCT	16	6–14		Milk + omalizumab	10	Avoidance	6
Mota et al,[55] 2018	Portugal	RLS	42	2–18	40	Milk	42		
Kauppila et al,[8] 2019	Finland	RLS	244	≥5	42	Milk	244		
De Schryver et al,[56] 2019	Canada	RCT	52	6–18	44	Milk	26	Avoidance[a]	26
Patriarca et al,[57] 1998	Italy	RCT[b]	20	5–13	50	Egg (n = 5), milk (n = 6)	11	Avoidance	9
Patriarca et al,[58] 2003	Italy	CCT[b]	75	3–55	58	Egg (n = 15) Milk (n = 29)	59	Avoidance	16
Patriarca et al,[59] 2007	Italy	CCT[b]	52	3–16	42	Egg (n = 17) Milk (n = 18)	42	Avoidance	10
Morisset et al,[60] 2007	France	RCT	150	1–8	35	Egg (n = 51) Milk (n = 28)	79	Avoidance	71
Staden et al,[61] 2007	Germany	RCT	45	0.6–12.9	36	Egg (n = 11) Milk (n = 14)	11	Avoidance	20
Arasi et al,[62] 2019	Italy	RLS	96	4–14	64	Egg (n = 14), milk (n = 20), plan for AR	34	Egg (n = 27) Milk (n = 35) No plan for AR	62

[a] Start OIT after avoidance.
[b] OIT for several foods reported together.

Table 3
Safety reporting in peanut, walnut, sesame, and wheat oral immunotherapy studies reviewed

Study	Differential Reporting During Phases	Report Total Doses Given	Report AR per Dose	Report Pt. per AR	% Pts Reached Maintenance Dose	% Pts Withdrawn for AR	Report Accidental Reactions in Controls
Peanut OIT							
Varshney et al,[14] 2011	Yes	No	No	Partially	84	16	No
Anagnostou et al,[15] 2014	No	Yes	Yes	Yes	84-91	5	No
Tang et al,[16] 2015	Yes	No	No	Yes	100	3.2	Yes
Narisety et al,[17] 2015	Yes	Yes	Yes	Yes	SLIT: 100 OIT: 91	SLIT 10; OIT 27 SLIT + OIT: 22.2	No
Kukkonen et al,[7] 2017	Yes	No	No	Yes	67 ITT; 83 PP	BU 10.3; M 12.9	No
Vickery et al,[18] 2017	Yes	No	Yes	Yes	86.5	8.1	No
Bird et al,[19] 2018	No	No	No	Yes	79	21	Yes
Fauquert et al,[20] 2018	No	No	Yes	Yes	81	9.5	Yes
Nagakura et al,[21] 2018	Yes	Yes	Yes	NM	92	NM	No
Vickery et al,[13] 2018	Yes	No	Yes	Yes	78	14	No
Nachshon et al,[22] 2018	Yes	No	No	Yes	78 (3000 mg) 92 (≥300 mg)	0.8	NA

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Table 3
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Study	Differential Reporting During Phases	Report Total Doses Given	Report AR per Dose	Report Pt. per AR	% Pts Reached Maintenance Dose	% Pts Withdrawn for AR	Report Accidental Reactions in Controls
Blumchen et al,[23] 2019	Yes	Yes	Yes	Yes	74.2	6.5	Yes
Reier-Nilsen et al,[24] 2019	No	Yes	Yes	Yes	21.1 full dose 54.4 partial dose	26.7	No
Wasserman et al,[25] 2019	Yes	No	No	Yes	78	12.6	NA
Soller et al,[26] 2019	Yes	Yes	Unclear	Yes	90	Unclear (<10)	NA
MacGinnitie et al,[27] 2017	No	Yes	Yes	Yes	88.8	8.6	Yes
Walnut OIT							
Elizur et al,[28] 2019	Yes	Yes	Yes	Yes	89	5.4	Yes
Sesame OIT							
Nachshon et al,[29] 2019	No	Yes	Yes	Yes	88.4	NM	No
Wheat OIT							
Nowak-Węgrzyn et al,[30] 2019	Yes	Yes	Yes	Yes	82.6 low dose 57.1 high dose	10.9	Yes

Abbreviations: BU, build-up phase; ITT, intention to treat population; M, maintenance phase; NA, nonapplicable; NM, no mention; PP, per protocol population; Pts, participants.

Table 4
Safety reporting in egg and milk oral immunotherapy studies reviewed

Study	Differential Reporting During Phases	Report Total Doses Given	Report AR per Dose	Report Pt per AR	% Pts Reached Maintenance Dose	% Pts Withdrawn for AR	Report Accidental Reactions in Controls
Egg OIT							
Burks et al,[31] 2012	No	Yes	Yes	No	87.5	15	Yes
Dello Iacono et al,[32] 2013	No	No	No	No	0 (90 partial dose)	0	Yes
Fuentes-Aparicio et al,[33] 2013	No	No	No	Yes	92.5	7.5	No
Meglio et al,[34] 2013	No	No	No	No	80	10	No
Vazquez-Ortiz et al,[35] 2014	Yes	Yes	Yes	Yes	80	18	Yes
Caminiti et al,[36] 2015	Yes	No	No	Yes	94.1	5.9	No
Escudero et al,[37] 2015	Yes	Yes	Yes	Yes	93.3	6.7	No
Pérez-Rangel et al,[38] 2017	Yes	No	Yes	Yes	94	3	Yes
Giavi et al,[39] 2016	Unclear	Unclear	Unclear	No	100	0	Yes
Itoh-Nagato et al,[40] 2018	No	No	No	Yes	93.3	11.1	NM
Machinena et al,[41] 2019	Yes	Yes	Yes	Yes	76.7	16.3	NA
Milk OIT							
Skripak et al,[42] 2008	No	Yes	Yes	Yes	92.3	7.7	Yes
Longo et al,[43] 2008	Yes	No	No	Yes	36 (54–<150 mL)	10	Yes
Caminiti et al,[44] 2009	No	No	No	Yes	70 (10–<200 mL)	20	NM
Pajno et al,[45] 2010	No	No	No	Yes	76.9 (7.7–<200 mL)	15.4	No
Martorell et al,[46] 2011	No	Yes	Yes	Yes	90	3.3	Yes
Salmivesi et al,[47] 2013	No	No	No	Yes	88 (1 y); 85 (3 y)	11.1	Yes

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Table 4
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Study	Differential Reporting During Phases	Report Total Doses Given	Report AR per Dose	Report Pt per AR	% Pts Reached Maintenance Dose	% Pts Withdrawn for AR	Report Accidental Reactions in Controls
Vázquez-Ortiz et al,[48] 2013	Yes	Yes	Yes	Yes	71.6 (20.9–<200 mL)	7.4	NA
Lee et al,[49] 2013	No	No	No	Yes	100	12.5	Yes
García-Ara et al,[50] 2013	Yes	No	No	Yes	92	5.5	Yes
Martínez-Botas et al,[51] 2015	No	Yes	Yes	Yes	100	0	NM
Yanagida et al,[52] 2015	No	Yes	Yes	No	58.3	0	No
Wood et al,[53] 2016	Yes	Yes	Yes	Yes	100 MOIT; 92.8 OIT	0 MOIT;14.3 OIT	NA
Takahashi et al,[54] 2017	Yes	Yes	AR per dose per Pt		100 MOIT	0	NM
Mota et al,[55] 2018	No	No	No	Yes	92.8	4.8	NA
Kauppila et al,[8] 2019	No	No	No	Yes	56	28	Yes
De Schryver et al,[56] 2019	Yes	No	No	Yes	73.2	26.8	Yes
Egg and milk OIT							
Patriarca et al,[57] 1998	No	No	No	Yes	CM 81.8; E 100	0	NM
Patriarca et al,[58] 2003	No	No	No	Yes	CM 65.5; E 83.3	CM 17; E 13.3	NM
Patriarca et al,[59] 2007	No	No	No	Yes	CM 66.7; E 83.3	CM 16.7; E 7.14	NM
Morisset et al,[60] 2007	No	No	No	No	CM 88.9; E 69.4	CM 11.1; E 14.3	NM
Staden et al,[61] 2007	No	No	No	Yes	64 (16 partial dose)	36	Yes
Arasi et al,[62] 2019	No	No	No	Yes	100	1	NA

Abbreviations: CM, milk; E, egg; MOIT, omalizumab and OIT.

Table 5
Symptoms and management of adverse reactions in the intervention group of peanut, walnut, sesame, and wheat oral immunotherapy studies reviewed

Study	Severity Grading	Skin	Oral	GI	Upper Respiratory	Lower Respiratory	Anaphylaxis	Epinephrine Use	Hospitalization ER, ICU
Peanut OIT									
Varshney et al,[14] 2011	No	NM	NM	NM	NM	NM	NM	10.5% Pt	No
Anagnostou et al,[15] 2014	No	13% Pt; 0.2% D	81% Pt; 6.3% D	Ab pain 57% Pt; 2.6% D	23% Pt; 0.4% D	23% Pt; 0.4% D	NM	2 = 1% Pt, 0.01% D	No
Tang et al,[16] 2015	No	41.2% Pt	0	11.7% Pt	0	44.2% Pt	9.7% Pt	9.7% Pt	No
Narisety et al,[17] 2015	Yes	2.8% D	24.2% D	9% D	6.9% D		9% Pt	36.3% Pt	No
Kukkonen et al,[7] 2017	Yes	Rash/eczema: BU 44%; M 18% Urticaria: BU 23% AE; M 24% AE	NM	Ab pain: BU 41%; M 18% Emesis: BU 10% AE; M 6% AE	NM	26% AE (BU) 21% AE (M)	0% AE (BU) 6% AE (M)	2.6% Pt	ER: BU: $4.6/10^4$ PtD M: $3/10^4$ PtD (28% Pt)
Vickery et al,[18] 2017[a]	Yes	Unclear >30 AE	Unclear	Unclear >57 AE	Unclear 20 AE	Unclear	Unclear	0.8% AE 6% Pt	No
Bird et al,[19] 2018	Yes	14% AE	10% AE	66% AE	48% AE		NM	3.4% Pt	1 SAE, 3.4% Pt
Fauquert et al,[20] 2018	Yes	81% AE	19% AE	76% AE	43% AE	57% AE	23.8% Pt 1/1000 D	9.5% Pt	No
Nagakura et al,[21] 2018	Yes	15.1% D	NM	28.6% D	15.1% D		NM	Hd 0% Hm 0.01% D	NM
Vickery et al,[13] 2018	Yes	66.9% AE	Pruritus 9.7% Pt	85.8% AE	81.2% AE		Unclear Systemic AR 14.2% Pt[b]	14% Pt	NM
Nachshon et al,[22] 2018	Yes	41% AE (BU)	NM	72% AE (BU)	41% AE (BU)	15% AE (BU)	Unclear	Hd 12.4% Pt Hm 14.5% FU 1.8%	No

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Table 5
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Study	Severity Grading	Skin	Oral	GI	Upper Respiratory	Lower Respiratory	Anaphylaxis	Epinephrine Use	Hospitalization ER, ICU
Blumchen et al,[23] 2019	Yes	60% Pt	40% Pt	26.7% Pt	NM	43.3% Pt	0.02% SAE	2/2 (100%) SAE	OIT: H 9.7% Pt PB: ER 3.2%; H 12.9% Pt
Reier-Nilsen et al,[24] 2019	Yes	75.4% Pt 0.8% AE	86% Pt 5.9% AE	84.2% Pt 6% AE	64.9% Pt 0.3% AE		19.4% Pt 0.06% AE	10.5% Pt 0.03% AE	NM
Wasserman et al,[25] 2019	Yes	NM	NM	37.4% Pt	NM	NM	23% Pt[c]	23% Pt	No
Soller et al,[26] 2019	Yes	NM	NM	NM (1.1% EoE)	NM	NM	Unclear	4.1% Pt	1.11% Pt
MacGinnitie et al,[27] 2017	Yes	NM	NM	NM (8.1%Pt EoE)	NM	NM	Unclear	Unclear[d]	NM
Walnut OIT									
Elizur et al,[28] 2019	Yes	Hd: 38%Pt 1% D	Hd 9%Pt <1% D	Hd 47%Pt 2% D	Hd 53%Pt 2% D	Hd 15%Pt 1% D	NM	BU 20% Pt M 15% Pt FU 2% Pt	NM
Sesame OI									
Nachshon et al,[29] 2019	Yes	26.8% Pt 1.25% D	NM	53.5% Pt 2.5% D	42.5% Pt 2% D	9.4% Pt 0.4% D	NM	Hd: 0.5% D; 16.7% Pt Home 8.3% Pt 0.05% D	NM
Wheat OIT									
Nowak-Węgrzyn et al,[30] 2019	Yes	2.5% AE	2.2% AE	6.4% AE	7.3% AE		NM	0.08% D	No

Abbreviations: Ab, abdominal; AE, adverse events; D, doses; ER, emergency room; FU, long-term follow-up; H, hospitalization; Hd, hospital dosing; Hm, home dosing; ICU, intensive care unit; PB, placebo; PtD, participant days.

[a] AEs presented in a figure; none of the multiple symptoms AE (n = 37) were considered anaphylaxis.

[b] Systemic allergic reactions in 14.2% Pt, mild 6.2% Pt, moderate 7.8% Pt, severe (considered anaphylaxis) 0.2% Pt.

[c] Epinephrine-treated reactions considered as anaphylaxis.

[d] Epinephrine needed in 14 reactions in 8 patients after 11 doses of omalizumab-OIT and 3 doses of OIT without omalizumab.

Table 6
Symptoms and management of adverse reactions in the intervention group of egg and milk oral immunotherapy studies reviewed

Study	Severity Grading	Skin	Oral	GI	Upper Respiratory	Lower Respiratory	Anaphylaxis	Epinephrine Use	Hospitalization ER, ICU
Egg OIT									
Burks et al,[31] 2012	Yes	4.4% D	15.4% D	5.5% D	7.8% D	No data	NM	No	No
Dello Iacono et al,[32] 2013	Yes	43.4% AE	39.6% AE	34% AE	32.1% AE	9.4% AE	NM	No	No
Fuentes-Aparicio et al,[33] 2013	No	16.7% AE	22.2% AE	58.3% AE	19.4% AE	25% AE	Unclear	12.5% Pt	No
Meglio et al,[34] 2013	Yes	30% Pt	50% Pt	50% Pt	0% Pt	30% Pt	No	NM	No
Vazquez-Ortiz et al,[35] 2014	Yes	20.5% AE	13.7% AE	37.2% AE	7.7% AE	18.8% AE	NM	26% Pt 0.1% D	NM
Caminiti et al,[36] 2015	Yes	5.9% Pt	0%	5.9% Pt	0%	0%	5.9% Pt	5.9% Pt	NM
Escudero et al, 2015[37]	Yes	B: 3.8% AE M: 9% AE 0.3% D	BU: 21.5% AE M: 53% AE 2.2% D	BU 82% AE M 44% AE 4% D	BU 11.4% AE M 24% AE 1.3% D	BU 6.3% AE 0.2% D	Unclear	3.3% Pt 0.04% D	No
Pérez-Rangel et al,[38] 2017	Yes	11% AE	19.4% AE	54.8% AE	7.7% AE	5.8% AE	1.3% AE	6.3% Pt	Unclear
Giavi et al,[39] 2016	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NM	No	No
Itoh-Nagato et al,[40] 2018	Yes	52.2% AE	NM	60% AE	52.2% AE	43.5% AE	2.2% AE	11.6% Pt	NM

(*continued on next page*)

Table 6
(*continued*)

Study	Severity Grading	Skin	Oral	GI	Upper Respiratory	Lower Respiratory	Anaphylaxis	Epinephrine Use	Hospitalization ER, ICU
Machinena et al,[41] 2019	Yes	NM	NM	NM	NM	NM	Unclear	13.9% Pt	No
Milk OIT									
Skripak et al,[42] 2008[a]	No	0.9% D	35.7% D	18.7% D	NM	8.1% D	1.2% D	0.2% D	No
Longo et al,[43] 2008	Yes	Hd 46.7% Pt Hm 23.3% Pt	Hd 100% Pt Hm 56.7% Pt	Hd 76.7% Pt Hm 46.7% Pt	Hd 60% Pt Hm 10% Pt	Hd 40% Pt Hm26.7% Pt	NM	Hd 13.3% Pt Hm 3.3% Pt	ER: 26.7% Pt
Caminiti et al,[44] 2009	No	10% Pt	20% Pt	30% Pt	30% Pt		30% Pt	20% Pt	No
Pajno et al,[45] 2010	No	7.7%Pt	15.4% Pt	38.5% Pt	30.8% Pt		23.1% Pt	15.4% Pt	No
Martorell et al,[46] 2011	Yes	67% Pt	NM	30% Pt	50% Pt		37% Pt	6.7% Pt	No
Salmivesi et al,[47] 2013	No	33.3%	44.4% Pt	50.5% Pt	11.1% Pt	19.2% Pt	0%	No	No
Vázquez-Ortiz et al,[48] 2013[b]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	8.7% AE 45.7% Pt	11.1% Pt 0.07%D	NM
Lee et al,[49] 2013	Yes	Unclear	Unclear	No	No	No	No	No	No
García-Ara et al,[50] 2013	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	3.3% Pt	No
Martínez-Botas et al,[51] 2015	Yes	17.4% AE	NM	33.3% AE	13.8% AE	48.7% AE	NM	NM	No
Yanagida et al,[52] 2015	Yes	Hd 3.6%D Hm 0.8%D	Hd 42.9% D Hm 13% D	Hd 5.3% D Hm 4.2% D	Hd 19.6% D Hm 4.3% D		NM	0% D	ER: 0.2% D
Wood et al,[53] 2016[c]	Yes	MOIT 0% D OIT BU 1.1 M 0.7%D	MOIT 0.6% D OIT BU 8.8% M 0.9% D	MOIT: 0% D OIT: BU 3%; M 0.4% D	MOIT: 0% D OIT: BU 2.5%; M 0.9% D		NM	No	No
Takahashi et al,[54] 2017	Yes	NM	NM	NM	NM	NM	NM	No	No

Mota et al,[55] 2018	Yes	40.5% Pt	9.5% Pt	11.9% Pt	9.5% Pt	11.9% Pt	4.8% Pt	4.8% Pt	No
Kauppila et al,[8] 2019[d]	No	HD 41% Pt LD 42% Pt	NM	HD 45% Pt LD 73% Pt	HD 40% Pt LD 69% Pt		Unclear	6.9%-14% Pt	ICU 0.4% Pt
De Schryver et al,[56] 2019	Yes	NM	NM	NM	NM	NM	15.8% AE	0.6 AE per Pt	ER: 3.8% Pt
Egg and milk OIT									
Patriarca et al,[57] 1998	No	CM 50% Pt HE 20% Pt	0%	CM16.7% Pt HE 20% Pt	0%	CM16.7% Pt HE 20% Pt	0%	No	No
Patriarca et al,[58] 2003	No	NM	NM	NM	NM	NM	NM	NM	No
Patriarca et al,[59] 2007	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NM	No
Morisset et al,[60] 2007	No	Unclear	NM	Unclear	Unclear	Unclear	Unclear	NM	NM
Staden et al,[61] 2007	No	Unclear	NM	Unclear	Unclear		NM	NM	No
Arasi et al,[62] 2019	Yes	NM	NM	NM	NM	NM	NM (0%)[e]	NM	NM

Abbreviations: CM, cow's milk; HE, hen's egg; Hm, home dosing.

[a] LRs considered as oral, multiple systems reactions included under anaphylaxis.

[b] AE presented in a figure; multisystem reactions included under anaphylaxis.

[c] Median percent of doses.

[d] Data of BU phase presented, 1 life-threatening anaphylaxis requiring ICU treatment.

[e] Outcome presented is severe AE with medication plan.

Reporting per organ/system affected (and also per individual symptoms) does not provide the whole picture, because some of these organs can be affected simultaneously in a single reaction, and this information is sometimes lacking or it is unclear how it is captured (as SR or anaphylaxis?). To overcome this problem, some studies[18,48] include a category of "multiple symptoms" or "multisystem" for single reactions that involved multiple systems and report reactions per organ only when they are affected separately. Some studies indeed reported on SR and only considered a subset of them as anaphylaxis.[13] Wasserman and colleagues[25] reported on "epinephrine-treated reactions," which have been considered to be equivalent to anaphylaxis, according to their criteria to recommend epinephrine use.[63]

There is also an important variability in the reporting of medications needed to control the reactions, with some studies providing frequency of the different drugs used, and others only providing the frequency of epinephrine use (the latter collected in **Tables 5** and **6**).

Safety information on the placebo-treated groups shows that the placebo intervention entails more side effects[13,16,19,23,27,30,31] than the mere avoidance, but it is unclear how this should be taken into account in the interpretation of safety data. Furthermore, accidental reactions in controls are reported in 48% of trials (see **Tables 3** and **4**).

Anaphylaxis

Anaphylaxis and GI reactions are the 2 main reasons to discontinue OIT for AR. In the 52 articles reviewed, anaphylaxis was not mentioned in 19 (37%); in 12 (23%), the reporting was unclear, and 21 (40%) provided a frequency in different ways (percent of adverse events, percent of patients treated, per dose; see **Tables 5** and **6**). Anaphylaxis seems not to be adequately captured and likely there is additional anaphylaxis that fulfills the current diagnostic criteria[64] under reactions reported as "systemic," and "multiple symptoms" or multisystem reactions. Even the studies reporting on "epinephrine-treated reactions"[25] may underestimate anaphylaxis with some of the criteria for epinephrine use.[63]

Who are the patients at risk of developing anaphylaxis during OIT? Multiple factors may contribute to the occurrence and severity of AR and anaphylaxis during OIT; some are related to the protocol, others to the patient, and also cofactors may play a role (reviewed in Ref.[65]). In studies on milk and egg OIT,[35,48] it has been found that a high level of sensitization, low threshold of reactivity, higher severity of the reaction in the entry food challenge, and underlying asthma are associated with a higher frequency and severity of reactions. Some casein immunoglobulin E (IgE)-binding peptides detected baseline have been associated with a poorer safety profile.[51] Cofactors like exercise, intercurrent infections, tiredness, nonsteroidal antiinflammatory drugs, and menses have been associated with anaphylaxis to doses tolerated previously.[65] Whether these cofactors contribute to the appearance and severity of the reaction or if they are merely coincidental is unclear. Other factors, like poor asthma or rhinitis control, dosing with an empty stomach, and irregular intake, have also been associated with a higher risk of reactions. Indeed, life-threatening reactions have been described in highly sensitized adolescents with uncontrolled asthma and suboptimal OIT compliance.[6,8]

In order to reduce the risk of AR, and especially, anaphylaxis, the effect of omalizumab has been studied.[27,53,54] Omalizumab seems to facilitate a rapid desensitization to peanut in highly sensitized patients[27] and improves the tolerance of milk OIT, with a significant reduction in the reaction rate per dose, in the number of reactions needing treatment, and in their severity, during both escalation and maintenance phases.[53,54] It

is not yet known how long it should be maintained, and once discontinued, some patients experience AR with the maintenance dose previously tolerated.[66]

Gastrointestinal Reactions

GI reactions are frequently reported and are very often the reason for discontinuation, in both controlled trials and RLS (see **Tables 5** and **6**). Some of these GI symptoms correspond to immediate-onset IgE-mediated reactions that appear shortly after dosing. However, there are also some recurrent GI symptoms independent of dose timing with associated blood eosinophilia. They have been described in RLS and consist mainly of episodic vomiting more than 2 hours after dosing, less frequently in abdominal pain, and no dysphagia nor food impacttion.[25,28,29,67] They have been named OIT-induced GI and eosinophilic responses[67] and later, eosinophilic esophagitis-like OIT-related syndrome (ELORS).[25] Controlled studies do not make a difference in reporting between these time-dependent and independent GI reactions, and it is thus not possible to establish the actual incidence rate and risk separately.

ELORS symptoms appear early in the course of OIT,[25,67] but resolution of symptoms and decrease of eosinophilia with dose reductions[22,24,25,28,29,67] and short courses (1–4 weeks) of proton pump inhibitors (PPI) have been reported,[24,25] allowing most patients to reach maintenance dose. The authors are not aware of data of endoscopies performed in those withdrawn from therapy, nor in those who responded to dose adjustments or PPI and could resume OIT. Some of these patients do not respond to dose reduction, and in the few that have undergone endoscopy, eosinophilic esophagitis (EoE) was confirmed.[67]

New-onset EoE has been described during OIT studies. A metaanalysis[68] of 9 studies on peanut, milk, and egg OIT published until March 2014 estimated that 2.7% (95% CI 1.7–4.0) of patients newly developed EoE. This metaanalysis synthesized data of 708 participants treated and 17 EoE events and documented a significant publication bias in favor of studies reporting EoE. Interestingly, Chu and colleagues[3] only found 3 events of new EoE in 719 patients undergoing peanut OIT and could not establish the treatment effect.

Long-Term Safety

Long-term safety information comes mainly from RLS and shows that most patients are able to consume the food with no or mild reactions, but also that severe anaphylaxis may appear to doses previously tolerated. Because of heterogeneity in reporting, it is difficult to establish the incidence rate. Kukkonen and colleagues[7] reported an annual incidence rate of emergency room visits during a median follow-up of 30 months of 11% or 3/10,000 patient-days; Vickery and colleagues[18] reported 0.06% adverse events per person per dose in a 1- to 3-year maintenance, and Wasserman and colleagues[25] reported 9.9 epinephrine-treated reactions per 100 patient-years, all 3 being studies on peanut OIT. However, there are patients lost to follow-up who might have experienced AR, and mild AR might have not been reported by patients, or are not captured.[25] The frequency and severity of reactions seem to decrease with longer maintenance.[25,69] The analysis of circumstances surrounding these reactions points to the implication of some cofactors in around half of the events, and providing safety precautions to patients/families entails a significant reduction in AR.[62] Although cofactors may contribute to the appearance or severity of reactions, it is very likely that patients exercise (for instance) in many other occasions without having a reaction, but that type of information is not captured. Reactions during home maintenance are very worrying for patients and clinicians, and the identification of patients at risk is another unmet need. Interestingly, Kauppila and

colleagues[8] found that high baseline milk-specific IgE and any GI or respiratory symptoms in the postbuildup phase were associated with milk anaphylaxis during maintenance.

SAFETY OF FOOD ORAL IMMUNOTHERAPY: WHAT ONE NEEDS TO LEARN

The lack of consistency in reporting adverse events in food OIT studies is the major limitation to establishing precisely the safety profile of this intervention, in the short and long terms. The authors still have open questions on when to start and end OIT, who are the best candidates with a good safety (and efficacy) profile that will most benefit from this intervention, and who are the higher-risk patients, in order to manage all of them adequately, with individualized care pathways.

Standardized Reporting of Safety

Because of the heterogeneity in reporting, it is not possible at present to estimate a rate per dose (or per 100 doses), a rate per patient, or exposure-adjusted rates, for adverse events in general, and for specific AR. In addition, besides reporting per organ/system involved, it is necessary to report on multisystem reactions and adequately identify anaphylaxis. Severity grading is also a parameter to include to provide a comprehensive view of AR, although a validated system accepted worldwide is not yet available.[9–12]

To overcome this problem, an international consensus on reporting structure for OIT studies is needed. It should involve multiple stakeholders, including clinicians, patients, and regulators, and the outcome could be an international guideline. Having a homogeneous reporting system will facilitate synthesis and metaanalysis of safety data, and identification of predictors of adverse events.

When to Start Oral Immunotherapy?

Most of the participants in OIT studies are children and adolescents, with adult patients included in some. There are no studies treating only adult patients, and a few studies[18,26,46,49] have exclusively treated infants and toddlers. For these reasons, in the European Academy of Allergy and Clinical Immunology guidelines on immunotherapy for FA,[4] no recommendation could be made on OIT for adult patients, and the recommendation for OIT to milk, egg, and peanut was for children "from around 4 to 5 years of age." This age recommendation was based on expert opinion, and not on scientific evidence. It is therefore important to establish whether OIT can be a potential treatment with an adequate safety and efficacy balance in adults, and in children less than 4 years of age, in order to know when to start OIT. In addition, it will be important to explore the interest, views, and compliance of adult patients, and parents of infants and toddlers submitted to OIT.

When To Stop Oral Immunotherapy?

In the frame of RCT, there are predefined criteria to discontinue therapy for safety reasons. In RLS, this is an individualized decision taken jointly by the allergy team with the patient and/or family. As previously reviewed, the main reasons to stop OIT are anaphylaxis and persistent, recurrent GI symptoms, although the frequency and severity of reactions that prompt discontinuation vary between studies. Severe anaphylaxis is a clear indication to stop OIT, but it could also be an indication to evaluate other therapeutic options, such as omalizumab.[66] There are patients experiencing anaphylaxis to a certain dose who have later completed the therapy[25] with dose adjustments, add-on medications to optimize control of atopic comorbidities

(essentially asthma, and seasonal rhinitis), and intensive patient/family education.[62] The same applies to persistent/recurrent GI symptoms.[22,24,25] Information coming from RLS with a large series of patients and a higher flexibility in the management has shown that dose adjustments with or without antihistamine and PPI allowed most patients with ELORS to complete the therapy. These patients would have probably been discontinued in RCT, and therefore, carefully documented observations coming from clinical practice contribute to improve the understanding of the reactions and the clinical management of patients.

The analysis of pooled data sets (including RLS), and new observation and controlled studies, together with the patients/parents' opinions, would help answering this question.

What Are the Patients' Needs and Opinions on Oral Immunotherapy?

Patients in general, and especially parents of food allergic children, have a remarkable adherence to OIT despite repeated AR. According to Dunn-Galvin and Hourihane,[70] from a patient's point of view, "expected" severe AR with OIT are well accepted because they produce less anxiety than uncertain potential accidental reactions with avoidance. Parents who perceived a significantly higher likelihood of their child having a severe reaction and dying if food is ingested were the ones willing to participate in OIT studies. In addition, acceptance may also be driven by the close follow-up during OIT. Further investigation is needed on patients/parents' preferences and views of risks and benefits of OIT.

Stratification of Patients' Risk and Development of Care Pathways

Not all the patients undergoing OIT have a similar risk, and it is clearly stated in some publications that a few patients experienced the most AR.[35,42,48,51] The appearance of an AR and its severity results from a combination of multiple factors (related to the protocol, intrinsic to the patient, cofactors) that has interactions or additive effects that are still not understood.[65,71] Some factors and potential biomarkers have been identified in some milk and egg OIT studies, but further studies are needed to validate them and look for new ones. It could be done by combining and analyzing already existing data sets and biological samples from RCT, CCT, and RLS in collaborative research. In addition, the generation of an international registry of OIT (systemic) adverse events, and new observation and controlled trials applying a standardized safety reporting would help to stratify the patients' risk, and analyzing the effect of protocol factors, cofactors, and use of adjuvants on OIT safety.

In summary, the analysis of large pooled clinical data sets with comprehensive and homogeneous safety reporting, together with integrated omics approaches in biological samples of the same individuals, may uncovered endo-phenotypes and stratify patients' risk. This approach, combined with the patients/parents' needs and opinions on OIT, will allow the development of safe(r) personalized patient-tailored treatment algorithms, which are lacking at present. They will give OIT the right place as a treatment option in FA.

DISCLOSURE

The institution of S. Vázquez-Cortés, P. Jaqueti, and M. Fernández-Rivas has received grants from Aimmune. M. Fernández-Rivas has received consultancy fees from Aimmune and DBV and lecture fees from Aimmune Therapeutics, ALK-Abello, Allergy Therapeutics, Diater, HAL Allergy, and Thermo Fisher Scientific. M. Alvaro-Lozano has received consultancy fees from Sanofi Genentech. S. Arasi and A. Machinena do not have any conflicts of interest to disclose.

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